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Determinants of Exercise Capacity in Patients With Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Reduced exercise capacity reflects symptom severity and clinical outcomes in patients with hypertrophic cardiomyopathy (HCM). The present study aimed to identify factors that may affect exercise capacity in patients with HCM.

Methods: In 294 patients with HCM and preserved left ventricular (LV) ejection fraction, we compared peak oxygen consumption (peak VO$_2$) evaluated by cardiopulmonary exercise testing as a representative parameter of exercise tolerance with clinical and laboratory data, including N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP), diastolic parameters on echocardiography, and the grade of myocardial fibrosis on cardiac magnetic resonance imaging (CMR).

Results: Median peak VO$_2$, was 29.0 mL/kg/min (interquartile range [IQR], 25.0–34.0). Age (estimated β = −0.140, $P < 0.001$), female sex (β = −5.362, $P < 0.001$), NT-proBNP (β = −1.256, $P < 0.001$), and E/e′ ratio on echocardiography (β = −0.209, $P = 0.019$) were significantly associated with exercise capacity. Peak VO$_2$ was not associated with the amount of myocardial fibrosis on CMR (mean of late gadolinium enhancement 12.25 ± 9.67%LV).

Conclusion: Decreased exercise capacity was associated with age, female sex, increased NT-proBNP level, and E/e′ ratio on echocardiography. Hemodynamic changes and increased filling pressure on echocardiography should be monitored in this population for improved outcomes.

Keywords: Exercise Capacity; Hypertrophic Cardiomyopathy; Myocardial Fibrosis

INTRODUCTION

Patients with hypertrophic cardiomyopathy (HCM) present with various symptoms, including exertional shortness of breath, chest pain, syncope, or pre-syncope.[1] Even with preserved left ventricular (LV) systolic function, patients with HCM often develop dyspnea or fatigue, and the majority of these patients have exercise intolerance.[2] In such cases, cardiopulmonary

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exercise testing (CPET) is an indicator of actual oxygen consumption and is a reliable method for objectively evaluating exercise capacity.[3]

Peak oxygen consumption (peak VO_2) has been reported to be a useful marker of functional capacity in HCM.[2] Exercise stress test is also an important and useful tool for evaluating symptoms and monitoring response to therapy in patients with HCM,[4] and it can aid in risk stratification for future events, as previously described.[5-7] Furthermore, evaluating exercise capacity could be a useful and simple way to assess hemodynamic status and clinical outcomes without the need for complex modalities in patients with HCM.[1,8] Previous studies have shown several parameters that are associated with exercise intolerance in patients with HCM.[8-15] However, few studies have conducted a comprehensive analysis of several parameters related to CPET, which can reliably demonstrate patients' functional capacity.

The aim of this study was to determine exercise capacity in patients with HCM via CPET and to evaluate the determinants of exercise capacity in clinical, laboratory, and imaging studies.

METHODS

Study population and clinical characteristics

The study was performed as a cross-sectional study using data from the observational HCM registry of the Samsung Heart Vascular Stroke Institute, Seoul, Korea, which consecutively enrolled 591 patients who were diagnosed with HCM and underwent cardiac magnetic resonance imaging (CMR) between 2008 and 2015. The study population comprised 294 patients with HCM who were able to perform CPET (n = 295) and presented with normal LV systolic function (ejection fraction ≥ 50%). CPET and CMR were performed according to a standard protocol at baseline.

Echocardiographic criteria for inclusion in the HCM registry were as follows: 1) posterior wall thickness ≥ 1.3, in the absence of any underlying clinical condition that could lead to LV hypertrophy (i.e., longstanding systemic hypertension, aortic or subaortic stenosis, and clinical evidence of metabolic infiltrative disease or inflammatory disease), an end-diastolic LV wall thickness of ≥ 15 mm at any site, or LV septal thickness; 2) posterior wall thickness ≥ 1.5, in patients with systemic hypertension or end-diastolic LV septal thickness; or 3) LV hypertrophy confined predominantly to the LV apex (only the apical four segments and the apical cap according to the 17-segment guidelines of the American Society of Echocardiography) with a maximal apical wall thickness of ≥ 14 mm or a ratio of maximal apical to posterior wall thickness ≥ 1.3 at end-diastole.[16] subjects with uncontrolled hypertension, uncontrolled ventricular arrhythmias, severe valvular diseases, other concomitant systemic diseases (including malignancy), and subjects who had poor echocardiographic windows for analysis were excluded.[1,17-19]

Clinical and laboratory evaluation

All clinical characteristics were obtained by reviewing the medical records. Symptoms were recorded, such as dyspnea (New York Heart Association [NYHA] functional classification) or chest pain. History of syncope or sudden cardiac death was recorded. Other past medical histories, which described the presence of hypertension, diabetes mellitus, or atrial fibrillation and information on family history of sudden cardiac death and HCM, were also reviewed. The family history was defined as history in first-degree relatives. We also obtained

the value of the biomarker N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) at the time of CPET; 24-hour Holter monitoring was performed for all subjects.

Echocardiographic study and CPET

Conventional two-dimensional echocardiography was performed, and echocardiographic parameters were obtained according to guidelines. LV end-diastolic and end-systolic volumes were measured from apical two- and four-chamber views, and the ejection fraction was calculated using the biplane modified Simpson's method. LV mass was calculated using the formula proposed by Devereux et al. and corrected by body surface area to derive the LV mass index.[20] The left ventricular outflow tract (LVOT) was scanned with continuous Doppler to measure the maximal velocity and estimated pressure gradient in apical three- or five-chamber views. LVOT obstruction was defined as a pressure gradient ≥ 30 mmHg at rest.[9,11,19,21,22]

Left atrial volume was measured using the biplane modified Simpson's method and adjusted for body surface area (left atrium volume index, LAVI). Early diastolic mitral annular velocity on the septal side (e) and peak early diastolic transmitral flow velocity (E) were measured, and E/e′ was calculated using these parameters.[23]

CPET was performed using the symptom-limited treadmill exercise test with respiratory gas exchange analysis in all patients using the Bruce protocol.[24-26] Twelve-lead electrocardiography was performed using conventional chest lead positioning before exercise and at the conclusion of each stage and after stress. Blood pressure (BP) was recorded every 2 minutes. Peak VO_2 was measured using a Medical Graphics metabolic cart (St. Paul, MN, USA). Peak VO_2 was the highest averaged 30-second VO_2 during exercise and was expressed as absolute or normalized peak VO_2 (percentage of age, sex, and weight predicted). Exercise was terminated if there was marked dyspnea, fatigue, chest discomfort, > 2-mm ST depression, or after completion of 15 minutes of the protocol (15.6 metabolic equivalents). Additionally, abnormal hemodynamic response to exercise was defined as follows: 1) blunted BP response, < 20 mmHg increase in systolic BP; or 2) hypotensive response, > 20 mmHg decrease in systolic BP from the baseline BP, or an initial increase in systolic BP followed by a decrease in systolic BP > 20 mmHg.[27,28]

CMR acquisition and analysis

CMR was performed using a 1.5 T system (Magnetom Avanto, Syngo MR B15 version; Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phased-array receiver coil during repeated breath-holding. The CMR protocol consisted of cine, T2W, first-pass perfusion, and late gadolinium enhancement (LGE) imaging. Cine imaging was performed with balanced steady-state free precession sequences along the long and short axes from the cardiac apex to the base of the LV. Cine images of steady-state free precession were obtained with adjacent short-axis slices (slice thickness, 6 mm; gap, 4 mm) to quantify LV function and volume.

Standard LGE imaging was performed as intravenously administered of gadobutrol (0.15 mmol/kg Gadovist; Bayer Healthcare, Berlin, Germany). LGE images were acquired from long-axial, short-axial, and apical 4-chamber views. These images used a multi-shot turbo field echo breath-hold sequence with a phase-sensitive inversion recovery method. The inversion time was usually 280–360 msec. LGE images were estimated 10 minutes after gadolinium administration. The field of view was 35 × 35 cm, and the field of matrix was 256 × 256 cm.[29] LGE was regarded present when the signal intensity of the index myocardial segment was greater than 6 standard deviations above the remote normal myocardial signal.

LGE volume was calculated by total summation of LGE coverage in all short-axis slices, which was demonstrated as the volumetric proportion of the total LV myocardium (%LV). CMR scans were visually interpreted by two experienced investigators who were blinded to the clinical and laboratory data.

Statistical analysis

Continuous variables were compared using Student's *t*-test or the Wilcoxon rank-sum test where applicable and are presented as mean ± standard deviation or median with interquartile range (IQR). Categorical data were analyzed using the Fisher exact test or χ^2 test, as appropriate.

We performed simple and multiple linear regression analyses to assess the relationship of relevant parameters with exercise capacity as a continuous variable. Simple correlations were analyzed using Spearman's correlation. All parameters were analyzed via multiple linear regression analysis (step 1) after univariable analysis. Parameters from the multiple regression analyses ($P < 0.2$) or clinically meaningful parameters were then entered into the final multiple linear regression model (step 2). These variables were calculated using a stepwise multiple linear regression analysis and included age, sex, NT-proBNP, and E/e′ ratio.

All analyses were conducted using R for Windows (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

Ethics statement

This study was approved by the Institutional Review Board of Samsung Medical Center, and the requirement for informed consent was waived (IRB No. 2015-12-136).

RESULTS

Baseline clinical characteristics

The baseline clinical characteristics of the subjects are shown in **Table 1**. There were 252 men (85.7%), and the median age of the population was 53 years (IQR, 46–61). Nineteen (6.5%) and 16 (5.4%) patients had a family history of HCM and a history of syncope, respectively.

Table 1. Clinical characteristics of the study population

Clinical parameters	Values	
Age, yr	52.52 ± 10.53	53 (46–61)
Male sex	252 (85.7)	
Family history of HCM	19 (6.5)	
Family history of sudden cardiac death	31 (10.5)	
History of syncope	16 (5.4)	
History of chest pain	53 (18.0)	
Past medical history		
- Atrial fibrillation	8 (2.7)	
- Hypertension	90 (30.6)	
- Diabetes mellitus	22 (7.5)	
- VT on holter (history of non-sustained or sustained VT)	34 (12.4)	
NYHA class ≥ II	54 (18.7)	
NT-proBNP, pg/mL	542.64 ± 629.61	295.35 (136.85–686.25)

Data are presented are number of patients (percent) and average ± standard deviation or median (interquartile range).
HCM = hypertrophic cardiomyopathy, VT = ventricular tachycardia, NYHA = New York Heart Association, NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide.

Fifty-four subjects (18.7%) complained of NYHA class ≥ II dyspnea. The mean NT-proBNP level was 542.64 ± 629.61 pg/mL.

CPET and CMR parameters

Echocardiographic, CPET, and CMR parameters are shown in **Table 2**. The mean maximum LV wall thickness was 17.47 ± 4.07 mm. Mean LAVI was 41.87 ± 16.43 mL/m^2 and the mean E/e′ ratio was 11.63 ± 4.34. LVOT obstructed was noted in 19 patients (16.7%).

Sixty-two (21.1%) patients had abnormal hemodynamic responses on CPET. Moreover, the median value of peak VO$_2$ as a representation of exercise tolerance was 29.0 mL/kg/min (IQR, 25.0–34.0) in the study population.

Mean amount of LGE on CMR was 12.25 ± 9.67%LV. LV ejection fraction and LV mass index on CMR were 69.68 ± 7.39% and 90.83 ± 29.01 g/m^2, respectively.

Table 2. The parameters of echocardiography, cardiopulmonary exercise test, and cardiac magnetic resonance on study population

Parameters	Mean ± SD	Median (range)
Type of HCM, No. of patients (%)		
Septal	94 (32.0)	
Apical	87 (29.6)	
Concentric	23 (7.8)	
Septal and apical	86 (29.3)	
Septal and anterior or septal and lateral (mixed)	4 (1.4)	
Baseline echocardiographic parameters		
Maximal LV wall thickness, mm	17.47 ± 4.07	17 (15–19.25)
Presence of LV outflow tract obstruction	49 (16.7)	
LV ejection fraction, %	66.07 ± 6.25	66 (61–70)
Left ventricle end-diastolic dimension, mm	48.56 ± 5.01	48.5 (45–52)
Left ventricle end-systolic dimension, mm	28.35 ± 3.88	29 (26–31)
Interventricular septum, mm	13.97 ± 5.02	12 (10–17)
LV posterior wall, mm	9.80 ± 1.77	10 (9–10)
Relative wall thickness	0.41 ± 0.10	0.39 (0.35–0.44)
LV mass index, g/m^2	123.26 ± 38.23	118.28 (97.22–143.52)
Left atrium size, mm	42.38 ± 6.28	42 (38–46)
Left atrium volume index, mL/m^2	41.87 ± 16.43	39 (31.35–47.23)
E velocity, m/s	0.62 ± 0.18	0.60 (0.49–0.72)
e′ velocity, m/s	0.057 ± 0.018	0.057 (0.044–0.070)
E/e′ ratio	11.63 ± 4.34	10.87 (8.60–13.33)
Cardiopulmonary exercise test parameters		
Exercise duration, min:sec	9:40 ± 2:15	9:56 (8:26–10:52)
Peak systolic blood pressure	171.11 ± 33.17	169 (151–191)
Peak heart rate	145.96 ± 21.50	148.5 (130.5–161)
Abnormal response of blood pressure (BP non-response)	62 (21.1)	
Peak VO$_2$ (mL/Kg/min)	29.39 ± 6.89	29 (25–34)
Baseline CMR parameters		
Late gadolinium enhancement (%LV) on CMR	12.25 ± 9.67	9.85 (5.17–17.12)
LV ejection fraction (%)	69.68 ± 7.39	70.42 (66.09–74.50)
Left ventricle end-diastolic volume (mL)	140.67 ± 83.83	133.70 (117.53–152.48)
Left ventricle end-systolic volume (mL)	41.49 ± 14.50	40.16 (32.29–48.31)
Stroke volume (mL)	95.07 ± 19.97	94.93 (81.80–104.80)
Cardiac output (L)	6.58 ± 3.45	6.13 (5.35–7.30)
LV mass index (g/m^2)	90.83 ± 29.01	85.37 (70.88–104.73)

Data are presented are number of patients (percent) and average ± standard deviation or median (interquartile range).
SD = standard deviation, HCM = hypertrophic cardiomyopathy, LV = left ventricular, BP = blood pressure, peak VO$_2$ = peak oxygen consumption, CMR = cardiac magnetic resonance.

Table 3. Simple linear regression analysis and simple correlation of exercise capacity

Variables	Simple linear regression			Simple correlation	
	Estimated β	Standard error	P value	r	P value
Age, yr	−0.138	0.037	< 0.001	−0.250	< 0.001
Female sex	−7.453	1.057	< 0.001	−0.350	< 0.001
Family history of HCMP	−0.692	1.589	0.664	−0.020	0.709
History of syncope	−2.130	1.585	0.180	−0.100	0.097
NYHA class ≥ II	−3.742	1.010	< 0.001	−0.220	< 0.001
NT-proBNP (pg/mL)	−0.004	0.001	< 0.001	−0.380	< 0.001
Maximal LV wall thickness (mm) on ECHO	−0.243	0.097	0.013	−0.170	0.003
Presence of LV outflow tract obstruction on ECHO	−3.220	1.057	0.003	−0.017	0.003
Left atrium volume index (mL/m²) on ECHO	−0.120	0.023	< 0.001	−0.260	< 0.001
E/e′ ratio on ECHO	−0.503	0.088	< 0.001	−0.270	< 0.001
Abnormal response of blood pressure (BP non-response) on CPET	−2.657	0.969	0.006	−0.160	0.007
Late gadolinium enhancement (%LV) on CMR	−0.059	0.039	0.137	−0.160	0.006
LV ejection fraction (%) on CMR	0.074	0.054	0.172	0.020	0.714
LV mass index (g/m²) on CMR	−0.022	0.014	0.114	−0.090	0.140

Simple correlation was analyzed by Spearman correlation method.
HCMP = hypertrophic cardiomyopathy, NYHA = New York Heart Association, NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide, LV = left ventricular, ECHO = echocardiography, CPET = cardiopulmonary exercise test, BP = blood pressure, CMR = cardiac magnetic resonance.

Univariate and multivariate analysis regarding exercise capacity

The association of various parameters with peak VO₂ in our study group is shown in **Table 3**. In univariate analysis with simple linear regression, several parameters were found to be associated with exercise tolerance, including age, sex, family history of HCM, history of syncope, NYHA class ≥ II, and increased NT-proBNP, echocardiographic parameters (LAVI, E/e′, maximal LV wall thickness, and the presence of LVOT obstruction), abnormal hemodynamic response on CPET, and various CMR parameters (LGE, LV ejection fraction, and LV mass index). Multiple linear regression analysis (step 1) revealed significant parameters, including age, female sex, NT-proBNP, and E/e′ ratio. The results of the stepwise multiple linear regression analysis (step 2) are shown in **Table 4**. Age (estimated β = −0.140, $P < 0.001$), female sex (β = −5.362, $P < 0.001$), NT-proBNP (β = −1.256, $P < 0.001$), and E/e′ ratio on echocardiography (β = −0.209, $P = 0.019$) were independent determinants of exercise capacity.

DISCUSSION

The principal finding of our study was that, on multivariate analysis, clinical variables (age, female sex), biomarker (NT-proBNP) elevation, and increased LV filling pressure (E/e′ ratio) were independent determinants of exercise capacity in patients with HCM. Among them, the significance of the E/e′ ratio is an important result in that it can be used very simply and usefully when following-up these patients in the real clinical field.

Parameters of LV diastolic dysfunction, especially E/e′, provide valuable information for determining exercise capacity in patients with heart failure symptoms.[30,31] Many studies have shown that patients with HCM have a spectrum of diastolic abnormalities, determined invasively or non-invasively, including increased LAVI, LV end-diastolic pressure (correlated with E/e′), and increased myocardial stiffness. Our study confirms that increased LV filling pressure is indeed related to decreased exercise capacity in relatively healthy HCM patients, regardless of the grade of myocardial fibrosis or presence of other prognostic indicators for hard events such as sudden cardiac death.

Table 4. Multiple linear regression analysis of variables for the correlation of exercise capacity (excluding 2 subjects as outliers)

Variables	Estimated β	Standard error	P value
Step 1			
Age, yr	−0.148	0.035	< 0.001[a]
Female sex	−5.454	1.185	< 0.001[a]
Family history of HCMP	1.164	1.454	0.424
History of syncope	−1.526	1.466	0.299
NYHA class ≥ II	−1.241	0.954	0.195[a]
NT-proBNP (pg/mL)	−0.870	0.446	0.052[a]
Maximal LV wall thickness (mm) on ECHO	−0.134	0.107	0.214
Presence of LV outflow tract obstruction on ECHO	−1.038	1.028	0.314
Left atrium volume index (mL/m²) on ECHO	−0.018	0.030	0.551
E/e′ ratio on ECHO	−0.201	0.096	0.037[a]
Abnormal response of blood pressure (BP non-response) on CPET	−0.971	0.889	0.275
Late gadolinium enhancement (%LV) on CMR	−0.010	0.039	0.797
LV ejection fraction (%) on CMR	0.022	0.049	0.657
LV mass index (g/m²) on CMR	0.007	0.016	0.670
Step 2			
Age, yr	−0.140	0.032	< 0.001
Female sex	−5.362	1.047	< 0.001
NYHA class ≥ II	−1.801	0.917	0.050
NT-proBNP, pg/mL	−1.256	0.342	< 0.001
E/e′ ratio on ECHO	−0.209	0.088	0.019

HCMP = hypertrophic cardiomyopathy, NYHA = New York Heart Association, NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide, LV = left ventricular, ECHO = echocardiography, CPET = cardiopulmonary exercise test, CMR = cardiac magnetic resonance.
[a]The stepwise multivariable linear regression analysis was performed with including the indicated parameters, and predictive MODEL was established as adjusting with parameters such as age, sex, NYHA class ≥ II, NT-proBNP, E/e′ ratio.

In previous studies, NT-proBNP level was associated with oxygen consumption in patients with HCM and was more notably influenced by functional impairment than by other conventional markers of disease severity. In accordance with the prior studies, we also found that elevated NT-proBNP level was also a significant determinate for exercise capacity in HCM. Many previous studies have reported that elevated NT-proBNP level shows correlation with LV filling pressure as E/e′ ratio on echocardiography.[32,33] Both parameters may serve as important indicators of LV functional reserve that affects exercise capacity in patients with HCM. Meanwhile, the association between female sex and reduced exercise capacity, as noted in our study, may possibly explain the relationship between the female sex and poor prognosis in previous studies.[34-36]

Hemodynamic compromise reflected by biomarker elevation and increased LV filling pressure could play a crucial role in exercise capacity in clinical practice and seems closely associated with a poor prognosis. For deciding management plans for patients with HCM, risk stratification for worse clinical outcomes and evaluation of subjective symptoms are both required. However, in real-world settings, patients may present with heart failure symptoms but also can be subjectively asymptomatic regardless of LV systolic function. Accordingly, self-reported subjective symptoms may be insufficient for critical decision making. Physiological exercise stress testing is recommended for patients with HCM because it provides customized exercise capacity and information related to exertional symptoms of heart failure,[37,38] allowing the exclusion of invasive procedures or substances such as contrast agents. We recommend that when exercise testing is performed, CPET should be performed with measurement of peak oxygen consumption as in our study in most patients with HCM to evaluate the patients' exercise capacity objectively. However, in patients who are unable to undertake such

exercise testing, surrogate markers such as parameters presented in our study may be useful for estimating the current status of patients with HCM. Furthermore, NT-proBNP and E/e′ ratio could be used as practical follow-up indicators to determine the treatment plan and medication use and to establish important policies for the treatment of HCM.

The mechanism responsible for diastolic dysfunction and elevated biomarkers might be multifactorial; the pathological changes in myocytes, such as hypertrophy and disarray, could increase passive LV stiffness. Fibrosis measured by LGE has been found to be associated with a poor clinical prognosis.[39-41] Furthermore, abnormal diastolic parameters may be associated with the progression of myocardial fibrosis.[42-45] Indeed, according to many previous studies, the amount of LGE on CMR and exercise capacity are both independent factors related to outcomes. Accordingly, we did anticipate that LGE and exercise capacity may show clinical correlation, which turned out to be not true in our study. However, in regard to hard outcomes, both parameters are independent factors showing independent associations. Furthermore, the prognostic value of LGE on CMR has been mostly reported to be associated with sudden cardiac death or ventricular arrhythmia rather than death from aggravation of heart failure, which may be more associated with functional capacity. Therefore, these parameters do not necessarily have to be related to each other, as there may be many confounding variables that exist between the parameters such as the pattern and shape of myocardial fibrosis represented by LGE. Additionally, as the patients enrolled in this study had various types of HCM, the amount of LGE may have had little effect on exercise capacity. This is because global changes that occurred in the LV—such as increase in LV filling pressure or diastolic dysfunction - rather than focal fibrosis should play larger roles in terms of exercise capacity.

This was a single-center cross-sectional study performed in a tertiary hospital. We only included patients who were able to exercise and had preserved LV systolic function, and we used an indirect outcome parameter to assess exercise capacity.

In our study, we could not conduct statistical prediction and assess the association of our parameters with clinical outcome. Although long-term clinical outcome is most important in clinical research, the purpose of our study was to identify parameters that were useful in the clinical field to predict the condition of HCM patients. We considered that exercise capacity would be helpful to predict and understand the overall condition and long-term course of HCM patients in the real-world clinical field. Additional studies should be performed for our parameters to be identified as factors that can predict the clinical composite outcome in HCM patients.

It is still controversial whether LV diastolic parameters at rest are major determinants of exercise tolerance in patients with HCM, and the true mechanism could still not be verified. Additionally, while we adjusted for many known determinants of exercise capacity, myocardial fibrosis assessed on CMR and the presence of LVOT obstruction did not have sufficient predictive ability. In our study, we only showed a simple correlation between exercise capacity and myocardial fibrosis and the presence of LVOT obstruction.

In patients with HCM and preserved LV systolic function, hemodynamic changes explained by biomarker (NT-proBNP) elevation and increased filling pressure (E/e′ ratio) and other clinical factors (age and female sex) were independent determinants of reduced exercise capacity, and they should be carefully considered while managing this patient population.

Further studies are needed to determine the prognostic value of peak oxygen consumption rate for predicting the risk of major cardiovascular events such as sudden cardiac death.

REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;287(10):1308-20.
   PUBMED | CROSSREF

2. Sharma S, Elliott P, Whyte G, Jones S, Mahon N, Whipp B, et al. Utility of cardiopulmonary exercise in the assessment of clinical determinants of functional capacity in hypertrophic cardiomyopathy. *Am J Cardiol* 2000;86(2):162-8.
   PUBMED | CROSSREF

3. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 2011;123(6):668-80.
   PUBMED | CROSSREF

4. Argulian E, Chaudhry FA. Stress testing in patients with hypertrophic cardiomyopathy. *Prog Cardiovasc Dis* 2012;54(6):477-82.
   PUBMED | CROSSREF

5. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346(11):793-801.
   PUBMED | CROSSREF

6. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CN, Lauer MS, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med* 2005;353(5):468-75.
   PUBMED | CROSSREF

7. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA* 2003;290(12):1600-7.
   PUBMED | CROSSREF

8. Desai MY, Bhonsale A, Patel P, Naji P, Smedira NG, Thamilarasan M, et al. Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging* 2014;7(1):26-36.
   PUBMED | CROSSREF

9. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348(4):295-303.
   PUBMED | CROSSREF

10. Finocchiaro G, Haddad F, Knowles JW, Caleshu C, Pavlovic A, Homburger J, et al. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. *JACC Heart Fail* 2015;3(5):408-18.
    PUBMED | CROSSREF

11. Peteiro J, Bouzas-Mosquera A, Fernandez X, Monserrat L, Pazos P, Estevez-Loureiro R, et al. Prognostic value of exercise echocardiography in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2012;25(2):182-9.
    PUBMED | CROSSREF

12. Peteiro J, Fernandez X, Bouzas-Mosquera A, Monserrat L, Méndez C, Rodriguez-Garcia E, et al. Exercise echocardiography and cardiac magnetic resonance imaging to predict outcome in patients with hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2015;16(4):423-32.
    PUBMED | CROSSREF

13. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. *Circ Heart Fail* 2012;5(4):535-46.
    PUBMED | CROSSREF

14. Bouabdallaoui N, Ennezat PV, Durand E, Puymirat E, Macron L. Late gadolinium enhancement cardiac magnetic resonance imaging in prognostic assessment of hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2013;14(10):1024.
    PUBMED | CROSSREF

15. Sorajja P, Allison T, Hayes C, Nishimura RA, Lam CS, Ommen SR. Prognostic utility of metabolic exercise testing in minimally symptomatic patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2012;109(10):1494-8.
    PUBMED | CROSSREF

16. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35(39):2733-79.
   PUBMED | CROSSREF

17. Elliott P. Hypertrophic cardiomyopathy. *Circulation* 2018;138(14):1399-401.
   PUBMED | CROSSREF

18. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004;363(9424):1881-91.
   PUBMED | CROSSREF

19. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42(9):1687-713.
   PUBMED | CROSSREF

20. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57(6):450-8.
   PUBMED | CROSSREF

21. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;114(21):2232-9.
   PUBMED | CROSSREF

22. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;58(25):e212-60.
   PUBMED | CROSSREF

23. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28(1):1-39.e14.
   PUBMED | CROSSREF

24. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol* 1991;17(6):1334-42.
   PUBMED | CROSSREF

25. Stewart RA, Kittelson J, Kay IP. Statistical methods to improve the precision of the treadmill exercise test. *J Am Coll Cardiol* 2000;36(4):1274-9.
   PUBMED | CROSSREF

26. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997;30(1):260-311.
   PUBMED | CROSSREF

27. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;33(7):2044-51.
   PUBMED | CROSSREF

28. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation* 1997;96(9):2987-91.
   PUBMED | CROSSREF

29. Kim EK, Lee SC, Hwang JW, Chang SA, Park SJ, On YK, et al. Differences in apical and non-apical types of hypertrophic cardiomyopathy: a prospective analysis of clinical, echocardiographic, and cardiac magnetic resonance findings and outcome from 350 patients. *Eur Heart J Cardiovasc Imaging* 2016;17(6):678-86.
   PUBMED | CROSSREF

30. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29(4):277-314.
   PUBMED | CROSSREF

31. Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, et al. Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. *Am J Cardiol* 2009;104(12):1727-31.
PUBMED | **CROSSREF**

32. Thaman R, Esteban MT, Barnes S, Gimeno JR, Mist B, Murphy R, et al. Usefulness of N-terminal pro-B-type natriuretic peptide levels to predict exercise capacity in hypertrophic cardiomyopathy. *Am J Cardiol* 2006;98(4):515-9.
PUBMED | **CROSSREF**

33. Tesic M, Seferovic J, Trifunovic D, Djordjevic-Dikic A, Giga V, Jovanovic I, et al. N-terminal pro-brain natriuretic peptide is related with coronary flow velocity reserve and diastolic dysfunction in patients with asymmetric hypertrophic cardiomyopathy. *J Cardiol* 2017;70(4):323-8.
PUBMED | **CROSSREF**

34. Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, et al. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;46(3):480-7.
PUBMED | **CROSSREF**

35. Geske JB, Ong KC, Siontis KC, Hebl VB, Ackerman MJ, Hodge DO, et al. Women with hypertrophic cardiomyopathy have worse survival. *Eur Heart J* 2017;38(46):3434-40.
PUBMED | **CROSSREF**

36. Choi YJ, Kim HK, Lee SC, Park JB, Moon I, Park J, et al. Validation of the hypertrophic cardiomyopathy risk-sudden cardiac death calculator in Asians. *Heart* 2019;105(24):1892-7.
PUBMED | **CROSSREF**

37. Suzuki K, Akashi YJ. Exercise stress echocardiography in hypertrophic cardiomyopathy. *J Echocardiogr* 2017;15(3):110-7.
PUBMED | **CROSSREF**

38. Sorensen LL, Liang HY, Pinheiro A, Hilser A, Dimaano V, Olsen NT, et al. Safety profile and utility of treadmill exercise in patients with high-gradient hypertrophic cardiomyopathy. *Am Heart J* 2017;184:47-54.
PUBMED | **CROSSREF**

39. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, et al. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;56(11):875-87.
PUBMED | **CROSSREF**

40. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;56(11):867-74.
PUBMED | **CROSSREF**

41. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;130(6):484-95.
PUBMED | **CROSSREF**

42. Hirota Y, Furubayashi K, Kaku K, Shimizu G, Kino M, Kawamura K, et al. Hypertrophic nonobstructive cardiomyopathy: a precise assessment of hemodynamic characteristics and clinical implications. *Am J Cardiol* 1982;50(5):990-7.
PUBMED | **CROSSREF**

43. Bonow RO, Frederick TM, Bacharach SL, Green MV, Goose PW, Maron BJ, et al. Atrial systole and left ventricular filling in hypertrophic cardiomyopathy: effect of verapamil. *Am J Cardiol* 1983;51(8):1386-91.
PUBMED | **CROSSREF**

44. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H, et al. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. *Prog Cardiovasc Dis* 1985;28(1):1-83.
PUBMED | **CROSSREF**

45. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;10(4):733-42.
PUBMED | **CROSSREF**